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Total Synthesis of the Cyanolide A Aglycon

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Supporting Information

ABSTRACT: The synthesis of the potent molluscicide cyanolide A has been achieved in 10 steps without the use of protecting groups. The synthesis features a key Sakurai macrocyclization/dimerization reaction that simultaneously forms both tetrahydropyran rings and the macrocycle of the natural product.

The C_2-symmetric macrodiolide cyanolide A was isolated by Gerwick and co-workers from the cyanobacteria *Lyngbya bouillonii* collected near Pigeon Island, Papua New Guinea.[1] The dimer exhibits significant molluscicidal activity against *Biomphalaria glabrata* (LC_{50} = 1.2 μM). This unique biological activity of cyanolide A and its interesting structure have inspired four total syntheses. All of the completed syntheses have relied on either Yamaguchi's or Shiina's lactonization protocol to form the macrocylic dimer from complex monomers (Figure 1).[2] Here we report an alternative synthesis of the cyanolide A aglycon in a concise process that avoids the use of protecting groups.

Cyanolide A is of particular interest in human health because of its molluscicidal activity; an effective and selective molluscicide agent has the potential to eradicate schistosomiasis, an endemic parasitic infection. More than 200 million people in developing countries have been infected, and more than 700 million people are at risk of this disease.[3] It is caused by a trematode flatworm (*Schistomosa*) that penetrates the skin and lays eggs in the bladder or bowels of the human host. An immune response to the eggs can cause a variety of symptoms, including hepatomegaly, splenomegaly, kidney disease, and bladder cancer.[4] The worm is carried by a variety of water snails that play host to the parasite, and it is transmitted to human hosts while they bathe in infected water sources.[5] Current therapy is heavily dependent upon treatment of infected individuals with the anthelmintic praziquantel.[6] Unfortunately, eliminating the parasite from the human host does not protect against future illness, and reinfection is common in patients who are repeatedly exposed to contaminated water. An alternative strategy to prevent schistosomiasis is elimination of the snail host through the use of molluscicides.[7] Regrettably, the mostly widely used molluscicide, niclosamide, has low water solubility and is detrimental to the environment.[8] The discovery and synthesis of an environmentally benign and cost-efficient molluscicide such as cyanolide A would therefore be useful in the eradication of this disease.

We recently disclosed a Prins dimerization/macrocyclization strategy to form similar tetrahydropyran-containing macrodiolides.[9,10] Unfortunately, the geminal dimethyl group at the 3-position of the THP ring of cyanolide A precludes the use of this strategy. Prins cyclizations that might form 3,3-disubstituted

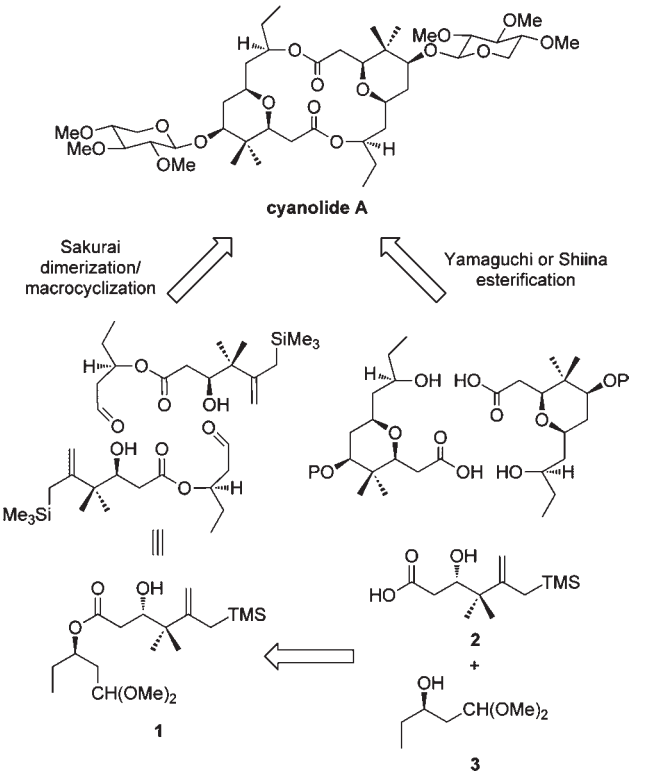
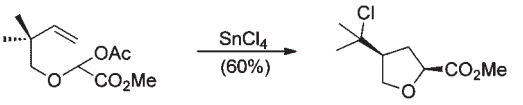


Figure 1. Retrosynthesis of cyanolide A.

THP rings are known to be diverted to tetrahydrofurans through either oxonia-Cope rearrangement followed by 5-exo cyclization or Wagner−Meerwein ring contraction of the tetrahydropyranyl cation (eq 1).[11] As a result, these ring systems are usually formed through either the intramolecular cyclization of elaborate linear molecules[2,12] or addition and reduction of lactone derivatives.[13]



(1)

Since the previously developed Prins reaction would be ineffective in the synthesis cyanolide A, it was proposed that a Sakurai reaction could be used to form the elusive 3,3-disubstituted THP rings while maintaining the simultaneous dimerization/macrocyclization strategy.[14] The activated allylsilane should stabilize the tetrahydropyranyl cation formed, preventing problematic rearrangements. On the basis of previous results

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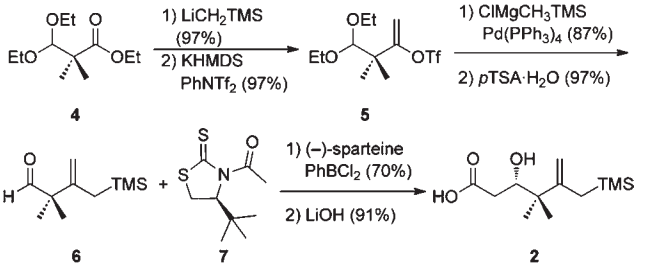
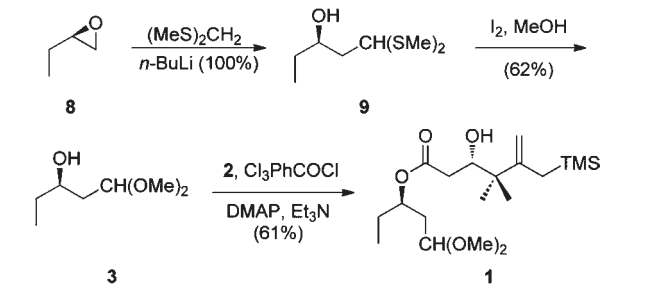
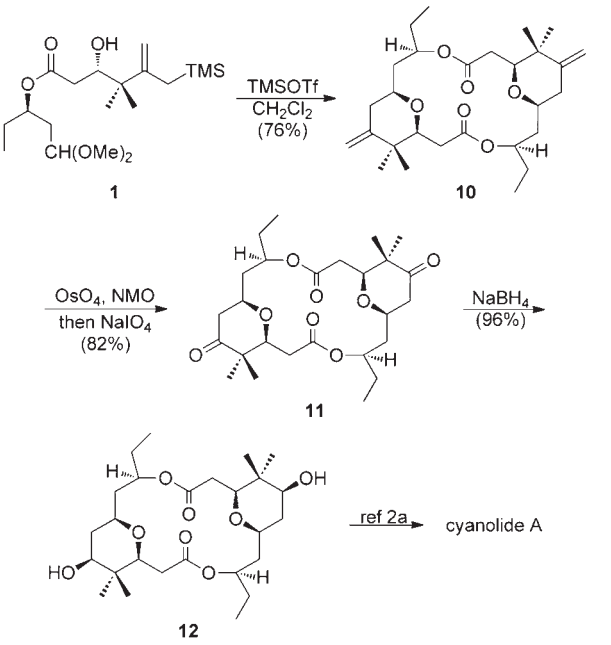
Scheme 1. Synthesis of β-Hydroxyacid 2



Scheme 2. Synthesis of Monomer 1



Scheme 3. Synthesis of Cyanolide A by a Sakurai Dimerization/Macrocyclization Reaction



concerning the synthesis of related dimeric macrolides, monomer **1** was identified as the ideal dimerization/macrocyclization precursor (Figure 1). It has been found that β-acyl aldehydes decompose rapidly under Lewis acidic conditions, so a dimethyl acetal was employed. The monomer would be formed from the esterification of alcohol **3** with β-hydroxy acid **2**.

The synthesis of β-hydroxy acid **2** began with ethyl 3,3-diethoxy-2,2-dimethylpropanoate (**4**), which was obtained in one step from commercially available materials (Scheme 1).[15] Cerium(III)-mediated addition to the ethyl ester would produce the allylsilane in one step, but unfortunately, addition to the hindered ester **4** was not possible.[16] Alternatively, formation of the methyl ketone followed by enol triflate formation afforded acetal **5** in good yield.[17] Kumada coupling followed by deprotection of the acetal under mildly acidic conditions produced aldehyde **6**. Standard aldol conditions using Nagao's auxiliary with either titanium tetrachloride or tin(II) triflate led exclusively to the proto-desilylated product. Fortunately, Sammakia's conditions utilizing dichlorophenylborane proved to be mild enough to provide the aldol adduct as a single diastereomer.[18] Finally, hydrolysis of the auxiliary provided β-hydroxy acid **2**.

Alcohol **3** was synthesized in two steps by addition of dimethyl thioacetal to (*R*)-1,2-epoxybutane (**8**)[19] followed by oxidation with iodine in the presence of methanol (Scheme 2). Esterification of alcohol **3** with β-hydroxy acid **2** was challenging, presumably because of the presence of the alcohol on **2**. Direct 4-dimethylaminopyridine (DMAP)-mediated acylation of alcohol **3** with the thiazolidinethione aldol adduct was unsuccessful.[20] Ultimately, Yamaguchi's esterification conditions provided the monomeric product in 61% yield.[21]

With the monomeric fragment in hand, further elaboration leading toward cyanolide A through Sakurai dimerization/macrocyclization was explored (Scheme 3).[22] When conditions developed for a Prins reaction (TESOTf in acetic acid) were employed,[9] a single product was isolated that was determined to be the trisubstituted endo olefin isomer of the desired product **10**. Similar isomerizations have been avoided by running Sakurai reactions at reduced temperatures in diethyl ether.[14a] Unfortunately, these conditions led to extensive decomposition of the starting material. After a variety of solvents, additives, and Lewis acids were screened, it was found that TMSOTf in dichloromethane at −78 °C provided a 76% yield of exo olefin dimer **10** with only a 7% yield of the inseparable endo product.[23] Upjohn dihydroxylation[24] of dimer **10** and subsequent oxidative cleavage yielded diketone **11**. Finally, reduction of the ketone afforded **12**, the known aglycon of cyanolide A. The spectroscopic data for this molecule closely matched the data from the previously reported syntheses, and glycosylation of the molecule to produce cyanolide A has been reported.[2a,b,d]

In summary, the total synthesis of the aglycon of cyanolide A has been completed with a longest linear sequence of 10 steps and 18% overall yield without the use of protecting groups. This marks the shortest synthesis reported to date. A key Sakurai dimerization/macrocyclization reaction was exploited to develop a significant amount of the molecular complexity in a single step. This strategy allowed facile formation of 3,3-disubstituted tetrahydropyrans, which has proved challenging in other approaches. Further applications of the dimerization/macrocyclization strategy are under development.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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